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1/77

28DEC02 E723529-3 D02934
P01/7700 0.00-0230088.7

Request for grant of a patent

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The Patent Office

Cardiff Road
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Gwent NP9 1RH

1. Your reference — 100939

2. Patent application number *(The Patent Office will fill in this part)* — 24 DEC 2002 — 0230088.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

07957251001

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)*

Thomas Miller

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

07822041001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	26
Claim(s)	8
Abstract	2
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date

Authorised Signatory 23/12/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

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Notes

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THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain pyrrole carboxamide compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

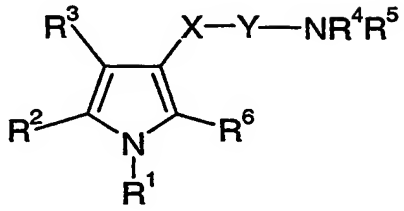
1,5 –Diarylpyrrole-3-carboxamides are reported to have antifungal activity in Il Farmaco 1988, vol XLIII, N9 665, M. Scalzo et al , Il Farmaco 1988, vol 43, N9 677, M. Scalzo et al , Il Farmaco 1989, vol 44, N1 65, C. G. Porretta et al , and Eur.J Med. Chem. 1992, 27, 701 F Cerretto et al. All compounds disclosed in these documents are disclaimed from the compound claims of the present application.

US 6,248,894 discloses certain pyrroles have anti-fungal activity. All compounds disclosed in this document are disclaimed from the compound claims of the present application.

WO01/ 58869 discloses that certain 1-(2-morpholinoethyl)pyrrolecarboxamides are useful in treating respiratory diseases.

Description of the invention

The invention relates a compound of formula (I)



I

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and

R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

X is CO or SO_2 ;

Y is absent or represents NH optionally substitututed by a C_{1-3}alkyl group;

R^4 and R^5 independently represent :

a C_{1-6}alkyl group;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

an optionally substituted non-aromatic C_{3-15}carbocyclic group;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

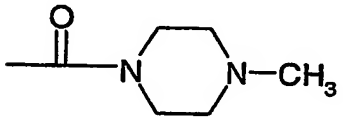
or R^4 represents H and R^5 is as defined above;

or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

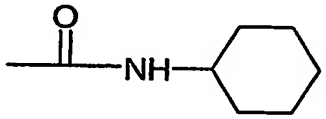
R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or

di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

with the proviso that when R^6 is methyl then the group $X\text{-}Y\text{-}NR^4R^5$ does not represent $CONHC_6H_{13}$, $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,



or



and with the further proviso that when R^1 and R^2 independently represent phenyl then Z is not an ortho methyl group.

Further values of R^1, R^2, R^3 , $X\text{-}Y\text{-}NR^4R^5$ and R^6 in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula I, R^1 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring. In such compounds R^1 is selected from phenyl , 4-chlorophenyl, 2, 4-dichlorophenyl and 4-methoxyphenyl.

In a second group of compounds of formula I, R^2 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring. In such compounds R^1 is selected from phenyl , 2, 4-dichlorophenyl and 2,4-dimethoxyphenyl.

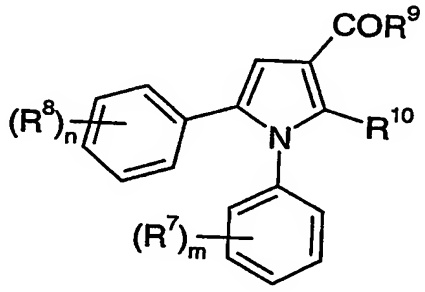
In a third group of compounds of formula I, $X\text{-}Y\text{-}NR^4R^5$ represents CONHPh or CONH(1--piperidyl).

In a fourth group of compounds of formula I, $X\text{-}Y\text{-}NR^4R^5$ represents CONH(1-piperidinyl).

In a fifth group of compounds of formula I, X-Y-NR^4R^5 represents CO(1-piperidinyl).

In a sixth group of compounds of formula I, R^6 represents methyl.

One group of compounds of the present invention relates to compounds of the general formula (II)



II

and pharmaceutically acceptable salts, prodrugs, and solvates in which

m represents 0,1, 2 or 3

R^7 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when m is 2 or 3 then the groups R^1 may be the same or different;

n represents 0,1, 2 or 3;

R^8 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when n is 2 or 3 then the groups R^2 may be the same or different;

R^9 represents 1-piperidinyl, 1-piperidinylamino or anilino wherein the phenyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy or halo; and

R^{10} represents a C_{1-6}alkyl, C_{1-6}alkoxy, or a C_{1-6}alkylamino group;
with the proviso that the compound is not 1-{[1-(4-chlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine or 1-{[1-(2,4-dichlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine.

Further values of R^7, R^8, R^9, R^{10} in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula II, m is 2 and the groups R^7 are located in the 2 and 4 positions of the phenyl ring. In such compounds R^7 is selected from chloro and methoxy and the groups R^7 may be the same or different.

In a second group of compounds of formula II, n is 2 and the groups R^8 are located in the 2 and 4 positions of the phenyl ring. In such compounds R^8 is selected from chloro and methoxy and the groups R^8 may be the same or different.

In a third group of compounds of formula II, R^9 represents anilino.

In a fourth group of compounds of formula II, R^9 represents 1-piperidinyl.

In a fifth group of compounds of formula II, R^9 represents 1-piperidinylamino.

In a sixth group of compounds of formula II, R^{10} represents methyl.

"Pharmaceutically acceptable salt", where such salts are possible, include pharmaceutically acceptable acid addition salt. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is

sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are:

2-methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide;
1-(4-chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;
1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;
1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;
1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;
2-methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
1-(4-chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
1-(4-methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
1-{[5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide; and
5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;
1-[(2-methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine;
1-{[1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-{[1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

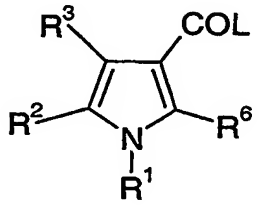
1-{[5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I in which X is CO may be prepared by reacting a compound of formula III



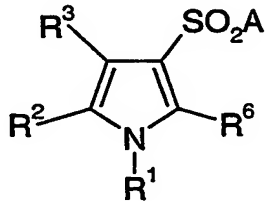
III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo e.g.chloro, with an amine of formula IV

$R^4R^5YNH_2$ IV

in which R^4 and R^5 are as previously defined in an inert solvent, for example dichloromethane, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, or optionally in the presence of a base for example triethylamine, at a temperature in the range of -25°C to 150°C, and when L is hydroxy optionally in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Compounds of formula I in which X is SO_2 may be prepared by reacting a compound of formula V



V

in which R^1, R^2, R^3 and R^6 are as previously defined and A represents halo with an amine of formula IV

$$R^4R^5YNH_2 \qquad IV$$

in an inert solvent, for example dichloromethane, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, at a temperature in the range of -25°C to 150°C.

Compounds of formula III may be prepared as described in the Examples and by other methods known to those skilled in the art. Certain compounds of formula III are novel and are claimed as a further aspect of the present invention as useful intermediates.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutically acceptable organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

A compound of the invention may also be combined with other anti-obesity agents such as Orlistat or a monoamine reuptake inhibitor, for example Sibutramine. Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in

the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I including the compounds in the provisos in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders,

schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I including the compounds in the provisos to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Examples

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

Abbreviations

DCM - dichloromethane

DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA – triethylamine

TFA – trifluoroacetic acid

DMSO	dimethyl sulfoxide
t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublets

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^{1}H NMR measurements were performed on a Varian Inova 500, operating at ^{1}H frequency 500 MHz. Chemical shifts are given in ppm. Purifications were performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. As the mobile phase, acetonitrile and buffered phase (0.1 M NH_4Ac:acetonitrile 95:5) were used.

Alternative

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Synthesis of intermediates

Preparation A

The following intermediates were prepared according to Scalzo, M. et al., Farmaco, Ed. Sci. (1988), 43(9), 665-676.

(a) Ethyl 2-acetyl-4-oxo-4-phenylbutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.98 (d, 2H), 7.65 (t, 1H), 7.53 (t, 2H), 4.13 (m, 3H), 3.56 (ddd, 2H), 2.32 (s, 3H), 1.18 (t, 3H).

(b) Ethyl 2-acetyl-4-(2,4-dichlorophenyl)-4-oxobutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.81-7.54 (m, 3H), 4.20-4.10 (m, 3H), 3.52-3.39 (m, 2H), 2.30 (s, 3H), 1.18 (t, 3H).

(c) Ethyl 2-acetyl-4-(2,4-dimethoxyphenyl)-4-oxobutanoate

^{1}H-NMR ($(CD_3)_2SO$) δ 7.68 (dd, 1H), 6.67 (s, 1H), 6.61 (m, 1H), 4.10 (m, 3H), 3.91, (d, 3H), 3.84 (d, 3H), 3.41 (m, 2H), 2.28 (d, 3H), 1.17 (dt, 3H). MS *m/z* 309 $(M+H)^+$.

Preparation B

The following intermediates were prepared essentially as described: Scalzo, M. et al., Farmaco, Ed. Sci. (1988), 43(9), 665-676. As recognised by those skilled in the art, the compounds described in Preparation A were, together with the appropriately substituted aniline, used as starting materials.

(a) Ethyl 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate

Toluene-4-sulphonic acid monohydrate (13 mg, 0.075 mmol) was added under nitrogen to a solution of aniline (0.43 mL, 4.7 mmol) and ethyl 2-acetyl-4-oxo-4-phenylbutanoate (Preparation A (a), 1.16 g, 4.7 mmol) in ethanol (55 mL). The mixture was refluxed for 20h, then evaporated. The crude product (1.22 g) was used in the next step without further purification. MS *m/z* 306 $(M+H)^+$.

(b) Ethyl 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.61 g) was used in the next step without further purification. MS *m/z* 340 $(M+H)^+$.

(c) Ethyl 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.68 g) was used in the next step without further purification MS *m/z* 336 $(M+H)^+$.

(d) Ethyl 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.55 g) was used in the next step without further purification. MS *m/z* 374 $(M+H)^+$.

(e) Ethyl 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (1.32 g) was used in the next step without further purification. MS *m/z* 408 $(M+H)^+$.

(f) Ethyl 5-(2,4-dichlorophenyl)- 1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate

The title compound was prepared as described in Preparation B (a).

The crude product (0.72 g) was used in the next step without further purification. MS *m/z* 404 $(M+H)^+$.

(g) Ethyl 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate
The title compound was prepared as described in Preparation B (a).
The crude product (0.33 g) was used in the next step without further purification. MS *m/z* 366 $(M+H)^+$.

(h) Ethyl 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate
The title compound was prepared as described in Preparation B (a).
The crude product (0.36 g) was used in the next step without further purification. MS *m/z* 400 $(M+H)^+$.

(i) Ethyl 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate
The title compound was prepared as described in Preparation B (a).
The crude product (0.37 g) was used in the next step without further purification. MS *m/z* 396 $(M+H)^+$.

Preparation C

The title compounds described in Preparation B (a-i) were used as starting materials for the compounds described in Preparation C (a-i)

(a) 2-Methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid
Sodium hydroxide (2.4 g, 60 mmol) was added to a solution of crude ethyl 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylate (from Preparation B (a), 1.22 g, 4.0 mmol) in ethanol (25 mL). The mixture was refluxed for 3h, then an additional portion of sodium hydroxide (0.20 g, 5.0 mmol) was added and the mixture was refluxed for an additional 90 min. The ethanol was evaporated, then HCl (75 mL, 2M aq) was added and the mixture was stirred for 7h. The acidic aqueous solution was extracted with EtOAc, the organic layer was washed with brine, dried ($MgSO_4$), filtrated and concentrated to give the crude product (0.95 g). The crude product was used in the next step without further purification. MS *m/z* 278 $(M+H)^+$.

(b) 1-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).
The crude product (1.2 g) was used in the next step without further purification. MS *m/z* 312 $(M+H)^+$.

(c) 1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).
The crude product (1.3 g) was used in the next step without further purification. MS *m/z* 308 $(M+H)^+$.

(d) 5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).
The crude product (0.44 g) was used in the next step without further purification. MS *m/z* 346 $(M+H)^+$.

(e) 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).
The crude product (1.12 g) was used in the next step without further purification. MS *m/z* 380 $(M+H)^+$.

(f) 5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).
The crude product (0.51 g) was used in the next step without further purification. MS *m/z* 376 $(M+H)^+$.

(g) 5-(2,4-Dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).
The crude product (0.26 g) was used in the next step without further purification. MS *m/z* 338 $(M+H)^+$.

(h) 1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid
The title compound was prepared as described in Preparation C (a).

The crude product (0.30 g) was used in the next step without further purification. MS *m/z* 372 $(M+H)^+$.

(i) 5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid

The title compound was prepared as described in Preparation C (a).

The crude product (0.34 g) was used in the next step without further purification. MS *m/z* 368 $(M+H)^+$.

Examples of the invention

Example 1

2-Methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide

The crude 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid (50 mg, 0.18 mmol) from Preparation C (a) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were dissolved in CH_2Cl_2 (2 mL) and DMF (0.030 mL). The solution was cooled to 0°C. A slurry of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.40 mmol) in CH_2Cl_2 (0.5 mL) and DMF (0.040 mL) was added dropwise. Aniline (0.046 mL, 0.49 mmol) in CH_2Cl_2 (0.5 mL) and was then added dropwise. The mixture was allowed to attain room temperature, and was stirred overnight. The mixture was diluted with CH_2Cl_2, washed with Na_2HCO_3 (sat, aq) and the phases were separated. The organic phase was concentrated and the residue was purified by semipreparative HPLC to give the title compound (33 mg, 52%).

^{1}H-NMR (CD_3OD) δ 7.65 (dd, 2H), 7.44 (m, 3H), 7.33 (t, 2H), 7.20 (m, 2H), 7.16-7.08 (m, 6H), 6.90 (s, 1H), 2.38 (s, 3H). MS *m/z* 353 $(M+H)^+$.

Example 2

1-(4-Chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (b) was used as described in Example 1 to give the title compound (31 mg,

50%). ^{1}H-NMR (CD_3OD) δ 7.65 (d, 2H), 7.45 (m, 2H), 7.33 (t, 2H), 7.22-7.08 (m, 8H), 6.90 (s, 1H), 2.40 (s, 3H). MS *m/z* 387 $(M+H)^+$.

Example 3

1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (c) was used as described in Example 1 to give the title compound (20 mg, 32%). ^{1}H-NMR (CD_3OD) δ 7.65 (d, 2H), 7.33 (t, 2H), 7.18-7.08 (m, 8H), 6.97 (m, 2H), 6.88 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H). MS *m/z* 383 $(M+H)^+$.

Example 4

5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (d) was used as described in Example 1 to give the title compound (9 mg, 15%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.39-7.30 (m, 6H), 7.23 (d, 1H), 7.17 (m, 3H), 7.10 (dt, 1H), 6.84 (s, 1H), 2.40 (s, 3H). MS *m/z* 421 $(M+H)^+$.

Example 5

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (e) was used as described in Example 1 to give the title compound (3 mg, 5%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.41-7.36 (m, 3H), 7.32 (t, 2H), 7.27 (d, 1H), 7.23 (dd, 1H), 7.17 (m, 2H), 7.10 (t, 1H), 6.85 (s, 1H), 2.42 (s, 3H). MS *m/z* 455 $(M+H)^+$.

Example 6

5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (f) was used as described in Example 1 to give the title compound (15 mg, 25%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.38 (d, 1H), 7.32 (t, 2H), 7.22 (t, 1H), 7.19 (dd, 1H), 7.09 (m, 3H), 6.89 (m, 2H), 6.82 (s, 1H), 3.78 (s, 3H), 2.38 (s, 3H). MS *m/z* 451 $(M+H)^+$.

Example 7

5-(2,4-Dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (g) was used as described in Example 1 to give the title compound (20 mg, 33%). ^{1}H-NMR (CD_3OD) δ 7.64 (dd, 2H), 7.36-7.24 (m, 5H), 7.15-7.06 (m, 4H), 6.65(s, 1H), 6.43 (dd, 1H), 6.28 (d, 1H), 3.73 (s, 3H), 3.42 (s, 3H), 2.38 (s, 3H). MS *m/z* 413 $(M+H)^+$.

Example 8

1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (h) was used as described in Example 1 to give the title compound (39 mg, 65%). ^{1}H-NMR (CD_3OD) δ 7.63 (d, 2H), 7.32 (m, 4H), 7.17-7.06 (m, 4H), 6.65(s, 1H), 6.46 (dd, 1H), 6.31 (d, 1H), 3.75 (s, 3H), 3.44 (s, 3H), 2.39 (s, 3H). MS *m/z* 447 $(M+H)^+$.

Example 9

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide

Crude 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (i) was used as described in Example 1 to give the title compound (44 mg, 73%). ^{1}H-NMR (CD_3OD) δ 7.63 (d, 2H), 7.32 (t, 2H), 7.09 (m, 2H), 7.00 (d, 2H),

6.85 (d, 2H), 6.62(s, 1H), 6.42 (dd, 1H), 6.31 (d, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 2.36 (s, 3H). MS *m/z* 443 $(M+H)^+$.

Example 10a

2-Methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 10b

1-[(2-Methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine

The crude 2-methyl-1,5-diphenyl-1*H*-pyrrole-3-carboxylic acid (236 mg, 0.85 mmol) from Preparation C (a) and 4-dimethylaminopyridine (47 mg, 0.38 mmol) were dissolved in CH_2Cl_2 (5 mL) and DMF (0.142 mL) and 1-aminopiperidine (0.218 mL, 2.18 mmol) was added. The solution was cooled to 0°C. A slurry of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (360 mg, 01.88 mmol) in CH_2Cl_2 (2.4 mL) and DMF (0.189 mL) was added dropwise. The mixture was allowed to attain room temperature, and was stirred overnight. The mixture was diluted with CH_2Cl_2, washed with Na_2HCO_3 (sat, aq) and the phases were separated. The organic phase was concentrated and the residue was purified by semipreparative HPLC to give 10a (20 mg, 7%), and 10b (91 mg, 31%).

10a had: ^{1}H-NMR (CD_3OD) δ 7.41 (m, 3H), 7.20-7.04 (m, 7H), 6.68 (s, 1H), 2.84 (brs, 4H), 2.32 (s, 3H), 1.74 (m, 4H), 1.46 (brs, 2H). MS *m/z* 360 $(M+H)^+$.

10b had: ^{1}H-NMR (CD_3OD) δ 7.41 (m, 3H), 7.20-7.04 (m, 7H), 6.37 (s, 1H), 3.70 (t, 4H), 2.32 (s, 3H), 1.74 (m, 2H), 1.65 (brs, 4H). MS *m/z* 345 $(M+H)^+$.

Example 11a

1-(4-Chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 11b

1-{[1-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (b) was used as described in Example 10 to give the title compounds 11a (7 mg, 2%), and 11b (129 mg, 35%).

11a had: ^{1}H-NMR (CD_3OD) δ 7.43 (m, 2H), 7.20-7.04 (m, 7H), 6.67 (s, 1H), 2.83 (brs, 4H), 2.34 (s, 3H), 1.74 (m, 4H), 1.46 (brs, 2H). MS *m/z* 394 $(M+H)^+$.

11b had: ^{1}H-NMR (CD_3OD) δ 7.43 (m, 2H), 7.20-7.04 (m, 7H), 6.37 (s, 1H), 3.68 (t, 4H), 2.12 (s, 3H), 1.74 (m, 2H), 1.64 (brs, 4H). MS *m/z* 379 $(M+H)^+$.

Example 12a

1-(4-Methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

And Example 12b

1-{[1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (c) was used as described in Example 10 to give the title compounds 12a (43 mg, 10%), and 12b (174 mg, 43%).

12a had: ^{1}H-NMR (CD_3OD) δ 7.16-7.05 (m, 7H), 6.96 (d, 2H), 6.66 (s, 1H), 3.81 (s, 3H), 2.83 (brs, 4H), 2.50 (s, 3H), 1.74 (m, 4H), 1.45 (brs, 2H). MS *m/z* 390 $(M+H)^+$.

12b had: ^{1}H-NMR (CD_3OD) δ 7.16-7.05 (m, 7H), 6.95 (d, 2H), 6.35 (s, 1H), 3.81 (s, 3H), 3.70 (brs, 4H), 2.10 (s, 3H), 1.74 (m, 2H), 1.64 (brs, 4H). MS *m/z* 375 $(M+H)^+$.

Example 13a

5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide and Example 13b

1-{[5-(2,4-Dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (d) was used as described in Example 10 to give the title compounds 13a (7 mg, 3%), and 13b (52 mg, 20%).

13a had: ^{1}H-NMR (CD_3OD) δ 7.37-7.30 (m, 4H), 7.20-7.10 (m, 4H), 6.61 (s, 1H), 2.82 (brs, 4H), 2.35 (s, 3H), 1.73 (t, 4H), 1.45 (brs, 2H). MS *m/z* 428 $(M+H)^+$.

13b had: ^{1}H-NMR (CD_3OD) δ 7.38-7.30 (m, 4H), 7.15 (m, 4H), 6.34 (s, 1H), 3.70 (t, 4H), 2.15 (s, 3H), 1.75 (t, 2H), 1.64 (brs, 4H). MS *m/z* 413 $(M+H)^+$.

Example 14a

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 14b 1-{[1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (e) was used as described in Example 10 to give the title compounds 14a (17 mg, 3%), and 14b (144 mg, 22%).

14a had: ^{1}H-NMR (CD_3OD) δ 7.36 (m, 3H), 7.22 (s, 2H), 7.13 (m, 2H), 6.62 (s, 1H), 2.80 (brs, 4H), 2.35 (s, 3H), 1.72 (t, 4H), 1.44 (brs, 2H). MS *m/z* 462 $(M+H)^+$.

14b had: ^{1}H-NMR (CD_3OD) δ 7.37 (m, 3H), 7.20 (s, 2H), 7.15 (d, 2H), 6.34 (s, 1H), 3.69 (t, 4H), 2.15 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 447 $(M+H)^+$.

Example 15a

5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 15b 1-{[5-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (f) was used as described in Example 10 to give the title compounds 15a (24 mg, 8%), and 15b (69 mg, 23%).

15a had: ^{1}H-NMR (CD_3OD) δ 7.36 (s, 1H), 7.17 (s, 2H), 7.04 (d, 2H), 6.87 (d, 2H), 6.58 (s, 1H), 3.76 (s, 3H), 2.82 (brs, 4H), 2.37 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 458 $(M+H)^+$.

15b had: ^{1}H-NMR (CD_3OD) δ 7.37 (s, 1H), 7.15 (s, 2H), 7.06 (m, 2H), 6.88 (m, 2H), 6.31 (s, 1H), 3.77 (s, 3H), 3.69 (t, 4H), 2.13 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 443 $(M+H)^+$.

Example 16

1-{[5-(2,4-Dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (g) was used as described in Example 10 to give the title compound (83 mg, 54%).

^{1}H-NMR (CD_3OD) δ 7.34-7.20 (m, 3H), 7.07 (m, 3H), 6.40 (m, 1H), 6.27 (s, 1H), 6.15 (s, 1H), 3.70 (m, 7H), 3.39 (s, 3H), 2.14 (s, 3H), 1.73 (m, 2H), 1.63 (brs, 4H). MS *m/z* 405 $(M+H)^+$.

Example 17a

1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide and Example 17b 1-{[1-(4-Chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (h) was used as described in Example 10 to give the title compounds 17a (4 mg, 7%) and 17b (47 mg, 27%).

^{1}H-NMR (CD_3OD) for 17a: δ 7.31 (d, 2H), 7.07 (m, 3H), 6.43 (m, 2H), 6.30 (s, 1H), 3.74 (s, 3H), 3.41 (s, 3H), 2.80 (brs, 4H), 2.33 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 454 $(M+H)^+$.

^{1}H-NMR (CD_3OD) for 17b: δ 7.32 (d, 2H), 7.07 (m, 3H), 6.44 (m, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 3.74 (s, 3H), 3.69 (m, 4H), 3.41 (s, 3H), 2.14 (s, 3H), 1.72 (m, 2H), 1.62 (brs, 4H). MS *m/z* 439 $(M+H)^+$.

Example 18a

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide

and Example 18b 1-{[5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine

Crude 5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid from Preparation C (i) was used as described in Example 10 to give the title compounds 18a (45 mg, 22%), and 18b (92 mg, 56%).

18a had: ^{1}H-NMR (CD_3OD) δ 7.04 (d, 1H), 6.97 (m, 2H), 6.84 (m, 2H), 6.40 (m, 2H), 6.29 (d, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.48 (s, 3H), 2.82 (brs, 4H), 2.40 (s, 3H), 1.72 (m, 4H), 1.44 (brs, 2H). MS *m/z* 450 $(M+H)^+$.

18b had: ^{1}H-NMR (CD_3OD) δ 7.03 (d, 1H), 6.98 (m, 2H), 6.84 (m, 2H), 6.40 (dd, 1H), 6.30 (d, 1H), 6.11 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.69 (brs, 4H), 3.46 (s, 3H), 2.11 (s, 3H), 1.73 (m, 2H), 1.62 (brs, 4H). MS *m/z* 435 $(M+H)^+$.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is

demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

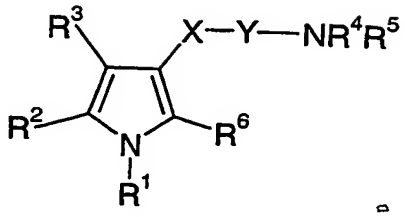
10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

Claims

1. A compound of formula (I)



I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which

R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and

R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, an aminoC_{1-3}alkyl group, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

X is CO or SO_2 ;

Y is absent or represents NH optionally substituted by a C_{1-3}alkyl group;

R^4 and R^5 independently represent :

a C_{1-6}alkyl group;

an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups;

an optionally substituted non-aromatic C_{3-15}carbocyclic group;

a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group;

a group $-(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

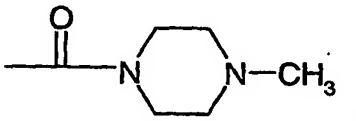
a group $-(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo;

or R^4 represents H and R^5 is as defined above;

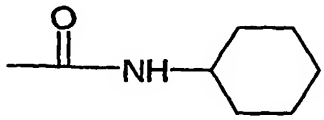
or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;

R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and;

with the proviso that when R^6 is methyl then the group X-Y-NR^4R^5 does not represent $CONHC_6H_{13}$, $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,



or



and with the further proviso that when R^1 and R^2 independently represent phenyl then Z is not an ortho methyl group.

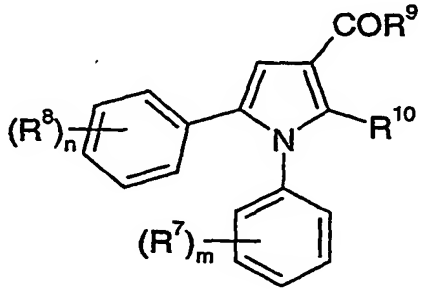
2. A compound according to claim 1 in which R^1 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring.

3. A compound according to any previous claim in which R^2 represents phenyl optionally substituted by halo or C_{1-3}alkoxy located in the 2 and 4 positions of the phenyl ring.

4. A compound according to any previous claim in which X-Y-NR^4R^5 represents CONHPh or CONH(1--piperidyl).

5. A compound according to any previous claim in which R^6 represents methyl.

6. A compound according to claim 1 of the general formula (II) in which



II

and pharmaceutically acceptable salts, prodrugs, and solvates in which

m represents 0,1, 2 or 3

R^7 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when m is 2 or 3 then the groups R^1 may be the same or different;

n represents 0,1, 2 or 3;

R^8 represents a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy, or halo wherein when n is 2 or 3 then the groups R^2 may be the same or different;

R^9 represents 1-piperidinyl, 1-piperidinylamino or anilino wherein the phenyl ring is optionally substituted by one or more of the following: a C_{1-6}alkyl group, trifluoromethyl, a C_{1-6}alkoxy group, difluoromethoxy, trifluoromethoxy or halo; and

R^{10} represents a C_{1-6}alkyl, C_{1-6}alkoxy, or a C_{1-6}alkylamino group;
with the proviso that the compound is not 1-{[1-(4-chlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine or 1-{[1-(2,4-dichlorophenyl)-5-phenyl-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine.

7. A compound according to claim 6 in which m is 2 and the groups R^7 are located in the 2 and 4 positions of the phenyl ring.

8. A compound according to claim 6 or claim 7 in which n is 2 and the groups R^8 are located in the 2 and 4 positions of the phenyl ring. In a third group of compounds of formula II, R^9 represents anilino.

9. A compound according to any one of claims 6, 7 or 8 in which R^9 represents 1-piperidinyl.

10. A compound according to any one of claims 6, 7, 8 or 9 in which R^9 represents 1-piperidinylamino.

11. A compound according to any one of claims 6, 7, 8, 9 or 10 in which R^{10} represents methyl.

12. A compound selected from:

2-methyl-*N*,1,5-triphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-*N*,5-diphenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-2-methyl-*N*,1-diphenyl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide;

2-methyl-1,5-diphenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-methoxyphenyl)-2-methyl-5-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-{[5-(2,4-dimethoxyphenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide; and

5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-*N*-piperidin-1-yl-1*H*-pyrrole-3-carboxamide;

1-[(2-methyl-1,5-diphenyl-1*H*-pyrrol-3-yl)carbonyl]piperidine;
1-{[1-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[5-(2,4-dichlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[5-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[1-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;
1-{[5-(2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl]carbonyl}piperidine;

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts and solvates thereof.

13. A compound of formula I as claimed in any previous claim for use as a medicament.

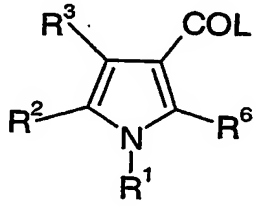
14. A pharmaceutical formulation comprising a compound of formula I, as defined in any one of claims 1 to 12 and a pharmaceutically acceptable adjuvant, diluent or carrier.

15. Use of a compound of formula I, as defined in any one of claims 1 to 12 including the compounds of the proviso in claim 1 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

16. A method of treating obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 12 including the compounds of the proviso in claim 1 to a patient in need thereof.

17. A compound as defined in any one of claims 1 to 12 including the compounds of the proviso in claim 1 for use in the treatment of obesity.

18. A process for the preparation of compounds of formula I in which X is CO comprising reacting a compound of formula III



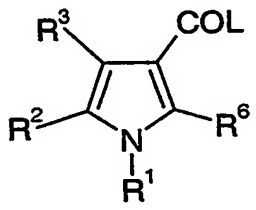
III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo with an amine of formula IV

$$R^4R^5YNH_2 \qquad IV$$

in which R^4 and R^5 are as previously defined in an inert solvent and optionally in the presence of a catalyst or optionally in the presence of a base at a temperature in the range of -25°C to 150°C, and when L is hydroxy optionally in the presence of a coupling agent.

19. A compound of formula III

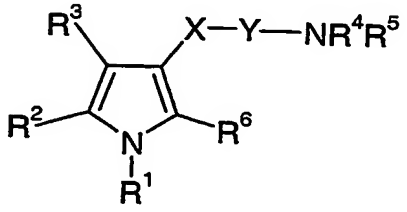


III

in which R^1, R^2, R^3, and R^6 are as previously defined and L represents hydroxy or halo.

ABSTRACT

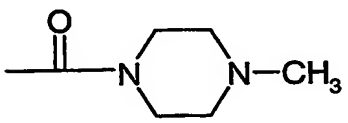
The present invention relates to a compound of formula I



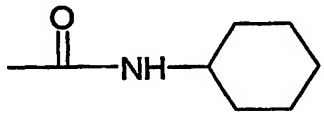
I

and pharmaceutically acceptable salts, prodrugs and solvates thereof, in which R^1 and R^2 independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z; Z represents a C_{1-3}alkyl group, a C_{1-3}alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C_{1-3}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl and acetyl; and R^3 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, an aminoC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula –CONHNR^aR^b wherein R^a and R^b are as defined for R^4 and R^5 respectively and; X is CO or SO_2 ; Y is absent or represents NH optionally substitututed by a C_{1-3}alkyl group;R^4 and R^5 independently represent :a C_{1-6}alkyl group; an (amino)C_{1-4}alkyl– group in which the amino is optionally substituted by one or more C_{1-3}alkyl groups; an optionally substituted non-aromatic C_{3-15}carbocyclic group; a (C_{3-12}cycloalkyl)C_{1-3}alkyl– group; a group –$(CH_2)_r$(phenyl $)_s$ in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z; naphthyl; anthracenyl; a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ;1-adamantylmethyl; a group – $(CH_2)_t$ Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C_{1-3}alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C_{1-5}alkyl group, a C_{1-5}alkoxy group or halo; or R^4 represents H and R^5 is

as defined above; or R^4 and R^5 together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C_{1-3}alkyl groups, hydroxy or benzyl ; R^6 is H, a C_{1-3}alkyl group, a C_{1-3}alkoxymethyl group, trifluoromethyl, a hydroxyC_{1-3}alkyl group, C_{1-3}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula $-CONHNR^aR^b$ wherein R^a and R^b are as defined for R^4 and R^5 respectively and; with the proviso that when R^6 is methyl then the group $X\text{-}Y\text{-}NR^4R^5$ does not represent $CONHC_6H_{13}$, $CONHC_{12}H_{25}$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$,



or



and with the further proviso that when R^1 and R^2 independently represent phenyl then Z is not an ortho methyl group; to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders particularly obesity, to methods for their therapeutic use and to pharmaceutical compositions containing them.